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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,840	03/13/2001	Gregory R. Mundy	10274-034001	4957

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FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,840	MUNDY ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,9,31,32 and 34-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,9,31,32 and 34-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/28/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 2/3/04, is acknowledged.

2. Claims 1-2, 4-5, 9, 31-32 and 34-41 are pending and under examination in the instant application.

3. The following new ground of objection is necessitated by the amendment submitted 2/3/04.

4. The amendment filed 2/3/04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment for incorporated by reference to "U.S. application U.S. Patent No. 5,840,299" on page 23, line 11 of the specification does not enjoy the status as part of the original disclosure in the application because the Patent No. 5,840,299 is not referred to in application as originally file. The Examiner notices that Applicant discloses that Patent No. 5,840,299 corresponded to the PCT/TJS95/01219. However, the Examiner is unable to determine that the Patent No. 5,840,299 corresponds to PCT/TJS95/01219.

Applicant is required to cancel the new matter in the response to this Office action.

5. Claim 1 is objected to because of the following informalities: "the" which recited in line 1 is not necessary. Appropriate correction is required.

6. In view of the amendment filed on 2/3/04, only the following rejections are remained.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 37 and 40-41 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 37 and 40-41 stand indefinite in the recitation of "L25" and "21.6", respectively because its characteristics are not known. The use of "L25" and "21.6" antibody homology as the sole means of identifying the claimed antibody renders the claim indefinite because "L25" and "21.6" are merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct antibody homolog.

Applicant's arguments, filed 2/3/04, have been fully considered, but have not been found convincing.

Applicant argues that "L25" is not "merely a laboratory designation" because the "L25" pre-priority date references refer to the specific anti-VLA-4 antibody. Regarding "21.6" antibody, Applicant argues that designation refers to a particular antibody, the identity and sequence of which was known in the art and disclosed in PCT/TJS95/01219 and corresponding U.S. Patent No. 5,840,299.

Contrary to applicant assertion such "L25" does not distinguish the antibody from other antibodies such as anti-HIV gp120 antibody as is evidenced by the Los Alamos national Laboratory web page. Similarly, 21.6 antibody is a laboratory designation and cannot be distinguished from other antibodies.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 34-41 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action mailed 7/30/03.

Applicant's arguments, filed 2/3/04, have been fully considered, but have not been found convincing.

Applicant argues the specification to include the number of the issued U.S. patent corresponding to the PCT publication already provided in the specification, which describes the making and using of murine 21.6 anti-VLA-4 antibody in detail, including the specific 21.6 sequences. Regarding "HP1/21", "HP2/1", "HP2/4", "L25", "P4C2" and "P4G9" antibody, Applicant argues that the recited antibodies were readily available to the public at the time of filing. Applicant argues that Exhibit 1 shows that the recited antibodies were Known in the art and available to the. In addition, Applicant submits, as Exhibit 2, four technical data sheets showing that at least HP2/1, P4C2, P4G9 and L25 were available from at least one commercial Source.

Regarding "21.6" antibody, the attempt to incorporate subject matter into this application by reference to PCT/US95/01219 is still improper, see above. Regarding commercially available antibodies, the Examiner notes that exhibit 2 provides that HP2/1, P4C2, P4G9 and L25 are commercially available from Chemicon International, Inc. and Becton Dickinson, however, the Chemicon International, Inc., technical data sheets restricted the use of the antibodies "For research use only; not for use as a diagnostic". Similarly, Becton Dickinson data sheet restricted the use of L25 antibody "For Research Use Only. Not for use in diagnostic or therapeutic procedures". Even though the HP2/1, P4C2, P4G9 and L25 are commercially available, the antibodies cannot be used in the method for the treating MM. Regarding, "HP1/2" and "HP2/4"

antibodies, biological materials must be known and readily available to the public (See MPEP 2404.01). Neither concept alone is sufficient. The fact that applicant and other members of the public were able to obtain the materials in question from publicly available resources prior to and after the filing date of the application does not establish the upon issuance of a patent on the application that such materials would continue to be accessible to the public.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-2, 4, 5, 9, 31-32 and 34-39 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Van Zaanen et al (Br. J. Haematol. 102:783-90, August 1998) in view of Masellis-Smith et al (IDS Ref No. AJ and Lokhorst et al (Blood 84:2269-2277, 1994) and Owens *et al* (1994) for the same reasons set forth in the previous Office Action, paper No. 12, mailed 11/04/02 for the same reasons set forth in the previous Office Action mailed 7/30/03.

13. Claims 34-39 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Van Zaanen et al (Br. J. Haematol. 102:783-90, August 1998) in view of Masellis-Smith et al (IDS Ref No. AJ and Lokhorst et al (Blood 84:2269-2277, 1994) and Owens *et al* as applied to claims 1-2, 4, 5, 9 and 31-32 above, and further in view of US Patent No. 5,932,214 A and Kamata et al (Biochem J. 305:945-951, 1995) for the same reasons set forth in the previous Office Action mailed 7/30/03.

Applicant's arguments, filed 2/3/04, have been fully considered, but have not been found convincing.

14. The declaration by Drs. Gregory Munday and Toshiyuki Yoneda under 37 CFR 1.131 filed 2/3/04 to entedate Van Zaanen *et al* reference is insufficient to overcome the rejections because the declaration fails to show that conception and completion of invention in this country or in a NAFTA or WTO member country. The Declaration is missing the limitation that the acts occurred in this country or in a NAFTA or WTO member country.

15. Claims 1-2, 4, 5, 9, 31-32 and 34-39 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,495,525 in view of U.S Patent No. 5,932,214 and Kamata *et al* for the same reasons set forth in the previous Office Action mailed 7/30/03.

Applicant's arguments, filed 2/3/04, have been fully considered, but have not been found convincing.

Applicant submits that a very broad range of immune and inflammatory disease in addition to multiple myeloma and tumor metastasis are encompassed in `525 patent.

However, the `525 patent teaches and claims the method of treating multiple myeloma (see patented claim 9, in particular).

Applicant argues that oMePUPA-V has an extraordinary broad range of therapeutic applicability, there is simply no indication in Lee or in any other reference cited that an antibody inhibitor of a4 integrins would have the same applicability.

The `525 patent further teaches anti-VLA-4 monoclonal antibodies which have been shown to inhibit VLA-4 dependent adhesion interactions both in vitro and in vivo. Further, the `525 patent administered the anti-VLA-4 antibody (PS/2) in activity in models of delayed type hypersensitivity. Further, the `525 patent teaches that the anti-VLA-4 antibody PS/2 inhibited swelling by approximately 30% whereas oMePUPA-V administered enterally was without effect in this model (see col., 22 lines 28-52, under example 3 in particular). Therefore, the `525 patent teaches anti-VLA-4 antibody that inhibited swelling in vivo which mimic the function of oMePUPA-V.

Regarding the motivation, Applicant argues that there is absolutely no motivation to select MM from this long list in Lee to treat with an antibody. Again, the `525 patent teaches and claims method of treating MM (see claim 9, in particular). Given the teachings of the `525 patent that the small molecule and anti-VLA-4 antibodies are capable of inhibiting VLA-4 mediated cell adhesion, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute oMEPUPA-V with anti-VLA-4 antibodies.

16. The declaration by Dr. Blake Pepinsky under 37 CFR1.132, filed on 2/3/04 is insufficient to overcome the rejection because: While the Declaration points out that oMePUPA-V is not interchangeable with anti-α4 integrin antibodies to treat MM. The Declaration states that it would have been unpredictable that an antibody against α4 integrins would have the same effect as any anti-VLA-4 small molecule. Further the Declaration states that Antibodies are completely different than small molecules. The Declaration points out that antibodies as a class of agents are vastly different in size than small molecule drugs such as oMePUPA-V. The Declaration states that due to small molecule drugs small size, a small molecule drug is typically directed to a "pocket" or specific docking site on the target molecule, where by the very nature it may act as either an agonist or an antagonist. In contrast, antibodies are large molecules and while they may bind to a particular epitope on a target, they effectively cover a large surface area and thereby act

to block a biological pathway through stearic hindrance, as opposed to binding a specific active site or pocket. However, the Examiner notes that the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though Declaration has proposed the mechanism by which an antibody would bind to VLA-4 to treat MM does not appear to distinguish the prior art teaching the same or nearly the same methods to achieve the same end result.

The Declaration states that unlike oMePUPA-V, an antibody-based therapeutic would be expected to implicate aspects of the immune response in its effect. The Declaration points to the Fc domain of antibodies of particular isotopes can bind to immune effector cells that express Fc receptors on their surface, allowing antibodies to recruit immune effector cells and complement factors to their site. The binding of some Fc receptors by antibodies provides signals that activate and recruit immune and inflammatory cells, whereas engagement of other Fc receptors can send inhibitory signals that down regulate immunity. The declaration states that The possible implicantion of such immune mechanisms with an anti-α4 integrin antibody could have been predicted to result in a completely different effect in vivo than that of oMePUPA-V. The Declaration concluded that a skilled practitioner would not have reasonably predicted that an anti-a4 integrin antibody would have the same effect as oMePUPA-V *in vivo*.

The Examiner realizes that difference between the antibodies and the small molecule drugs mechanism of action, however, the issue is the obviousness for one ordinary skill in the art at the time of the invention was made to use the VLA-4 inhibitor to treat MM. The `525 patent provides a method for treating multiple myeloma in a mammal comprising administering to a compounds which are capable of inhibiting VLA-4 mediated cell adhesion by inhibiting the binding of ligands to that receptor such as oMePUPA-V. Additionally, the `525 patent teaches that the compounds of the invention are inhibitors of VLA-4 integrin thereby blocking the binding of VLA-4 to its various ligand, such as VCAM-1 and regions of fibronectin. These compounds are useful in inhibiting cell adhesion processes, including cell activation, migration, proliferation and differentiation. The `525 patent further teaches anti-VLA-4 monoclonal antibodies which have been shown to inhibit VLA-4 dependent adhesion interactions both in vitro and in vivo. Therefore, the `525 suggested that suggests that anti-VLA-4 monoclonal antibodies agonists that mimic small molecule drugs can also be effective therapeutics. Furthermore, obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousnes. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). See MPEP 2143.02.

Finally, the declaration points to the an anti-α4 integrin antibody would not have been expected to have the same in vivo effect as oMePUPA-V, because anti-α4 integrin antibodies have a different specificity than oMEPUPA-V. The declaration states that Lee (`525 patent) teaches that oMePUPA-V is highly specific for VLA-4 but does not act on α4β7 integrin. The declaration points out that in contrast to the α4 integrin antibodies recited in the claims can bind both α4β1 and α4β7, implicating an additional integrin pathway. The declaration concluded that the broader specificity of an anti-a4 integrin, compared to oMePUPA-V, would have made it

unpredictable that an anti-α4 antibody would have the same effect as oMePUPA-V in vivo at al, much less have the same applicability across such a broad range of disorders and particularly against any one particular listed disorder, such as MM.

Again, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Furthermore, the Examiner notes that the recited antibodies in the claims binds specifically to α4 integrin subunit. While the anti-α4 antibodies may bind to α4β1 or α4β7, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Regarding the broad range of disorders, the `525 patent teaches and claims the method of treating multiple myeloma (see patented claim 9, in particular).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1-2, 4-5, 9 and 34-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 4-5 and 11 of copending Application No. 09/943,659. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 09/943,659 of Application `659 are drawn to the same method of treatment using the same composition comprising anti-alpha-4 antibodies. Further, the same product is used in the same method with same method steps and same patient populations, therefore the practice of the invention of `659 would necessarily result in the practice of the instant invention and vice versa.

Claims 34-39 are included because the anti alpha4 antibodies of `659 invention are considered to be H1/2, HP2/1, HP2/4, L25, P4C2, and P4G9 antibody homolog.

Applicant's arguments, filed 2/3/04, have been fully considered, but have not been found convincing.

Applicant indicates that once the present application deemed allowable, Applicant will address this rejection by canceling or amending the relevant claims of U.S.S. 09/943,659.

18. Claims 1-2, 4-5, 9 and 31-32 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 4-5, 9, 11-12, 17-8, 20-21, 25, 27, 34-35, 37 and 44 of copending Application No.10/086,217. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-2, 4-5, 9, 11-12 of Application `217 are drawn to the same method of treatment using the same composition comprising anti-alpha-4 antibodies. Further, while the preamble of the conflicting claims 17-8, 20-21, 25, 27, 34-35, 37 and 44 are different, the same product is used in the method with same method steps and patient populations, therefore the practice of the invention of `217 would necessarily result in the practice of the instant invention and vice versa.

Claim 12 of application `217 is included because the term "comprising" in the instant applicant opens up the composition to other unrecited materials such as those recited in claim 12 of application `217.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant indicates that once the present application deemed allowable, Applicant will address this rejection by canceling or amending the relevant claims of U.S.S. 10/086,217.

18. Claim 34-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 4-5, 9, 11-12, 17-8, 20-21, 25, 27, 34-35, 37 and 44 of copending Application No. 10/086,217 in view of U.S. Patent No. U.S Patent No. 5,932,214 and Kamata et al.

Applicant indicates that once the present application deemed allowable, Applicant will address this rejection by canceling or amending the relevant claims of U.S.S.N. 10/086,217.

19. No claim is allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
April 15, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600